

<b>Notice of Allowability</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/656,567	DAUGS, EDWARD D.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1.  This communication is responsive to 29 June 2006.
2.  The allowed claim(s) is/are 22-39.
3.  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a)  All
  - b)  Some\*
  - c)  None
 of the:
  1.  Certified copies of the priority documents have been received.
  2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3.  Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.  
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4.  A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5.  CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
  - (a)  including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
    - 1)  hereto or 2)  to Paper No./Mail Date \_\_\_\_\_.
  - (b)  including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6.  DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

#### Attachment(s)

1.  Notice of References Cited (PTO-892)
2.  Notice of Draftsperson's Patent Drawing Review (PTO-948)
3.  Information Disclosure Statements (PTO-1449 or PTO/SB/08),  
Paper No./Mail Date \_\_\_\_\_
4.  Examiner's Comment Regarding Requirement for Deposit  
of Biological Material
5.  Notice of Informal Patent Application (PTO-152)
6.  Interview Summary (PTO-413),  
Paper No./Mail Date \_\_\_\_\_.
7.  Examiner's Amendment/Comment
8.  Examiner's Statement of Reasons for Allowance
9.  Other \_\_\_\_\_.

**EXAMINER'S AMENDMENT**

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Since the election of the invention of Group III was made without traverse, the examiner is authorized to cancel nonelected claims at such time that claims drawn to the elected invention are in allowable form.

**IN THE CLAIMS –**

Claims 40 and 41 are **cancelled**.

end of amendment

***Response to Amendment***

As requested in the correspondence from applicants, filed 29 June 2006 (hereinafter “present amendment”), which is in reply to the Office action mailed 3 March 2006 (hereinafter “previous Office action”), claims 22, 24, 25, 29, 32 and 35 have been amended. In addition, paragraph [0142] in the specification has been replaced with the amended version thereof, as requested, and the abstract has been replaced with the amended version thereof, as requested.

***Status of Claim Rejections - 35 USC § 112***

In the previous Office action, claims 22-39 were rejected under 35 U.S.C. 112, second paragraph, for indefiniteness, on various grounds.

The terms “the racemic mixture “ and “the  $\alpha$ -(phenoxy)phenylacetic acid” in step (a) of claim 22 lacked antecedent basis, as there was no earlier recitation of those elements of step (a).

In view of the present amendment, this ground of rejection has been overcome.

In claim 24, the ratio specified was deemed ambiguous. In view of the present amendment, which more clearly specifies the two elements of the ratio, this ground of rejection has been overcome. Also in claim 24, the terms “first enantiomer” and “second enantiomer” were criticized, because it was not clear which was the desired enantiomer. In view of applicant’s argument, this ground of rejection is hereby withdrawn. As taught in the instant specification at page 12, paragraph [0074], the “first enantiomer” is the one concentrated in the solid phase, while the “second enantiomer” is concentrated in the solution phase.

Steps (i) and (ii) in claim 25 were found to be self-contradictory, because the two steps recited by raising and lowering of the temperature, since no order of steps (i) and (ii) was specified. The present amendment introduced the word "subsequently" at the beginning of (ii), obviating this ground of rejection. Step (ii), it is now clear, is conducted after step (i).

All rejections under 35 U.S.C. 112, second paragraph are hereby withdrawn.

***Status of Claim Rejections - 35 USC § 102***

In the previous Office action, claims 22, 23 and 27 were rejected under 35 U.S.C. 102(b) as being anticipated by US 6,262,118 (Luskey et al).

In view of the present amendment limiting the total amount of enantiomerically enriched chiral amine compound employed in step (a) of claim 22, the rejection is hereby withdrawn. Luskey et al provides no suggestion to employ an amount less than 0.5 molar equivalents of the enantiomerically enriched chiral amine compound.

***Status of Claim Rejections - 35 USC § 103***

In the previous Office action, claims 28-30 were rejected under 35 U.S.C. 103(a), as being obvious over Luskey et al, cited in the rejections under 35 U.S.C. 102.

Since the anticipation rejection based on Luskey et al has been overcome by the present amendment, the obviousness rejection based on the same reference is no longer tenable.

The rejection of claims 28-30 as being obvious over Luskey et al is hereby withdrawn.

***Abstract of the Disclosure***

The abstract was criticized in the previous Office action because the instant claims are no longer drawn to production of compounds of the formula described in the version of the abstract presented at the time of filing of the instant application.

Applicant has amended the abstract to correspond with the claimed subject matter.

***Allowable Subject Matter***

Claims 22-39 are allowed.

The present amendment, which limits the total amount of enantiomerically enriched chiral amine compound employed in step (a) of claim 22, from which all of the other claims depend, either directly or indirectly, has overcome the prior art rejections of record.

In the previous Office action, the closest prior art with respect to the instant claims was summarized on pages 8 and 9.

***Conclusion***

All Post-Allowance Correspondence concerning this application must be mailed to:

Mail Stop Issue Fee  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-872-9306, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027.

The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.

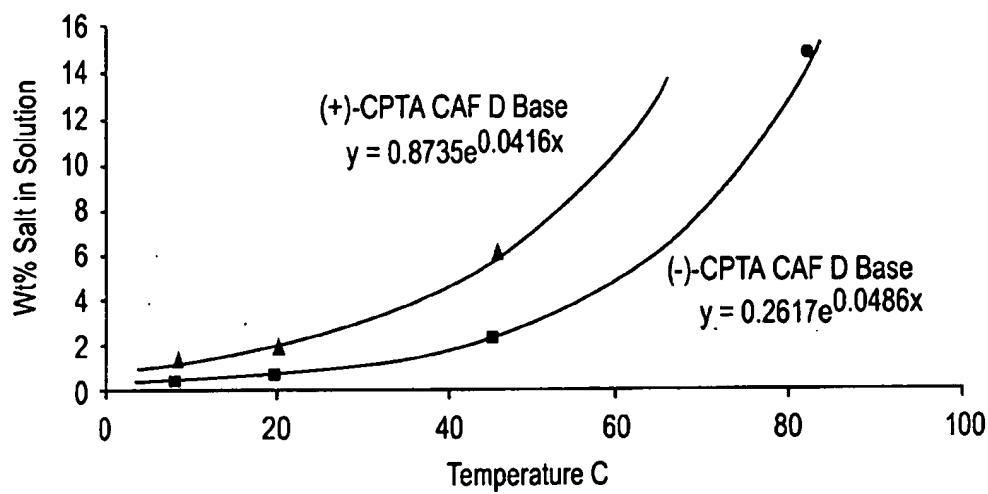
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A handwritten signature, appearing to read "Zarl", is written in black ink below the typed "zt".

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## REPLACEMENT SHEET

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**FIG. 1**

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## REPLACEMENT SHEET

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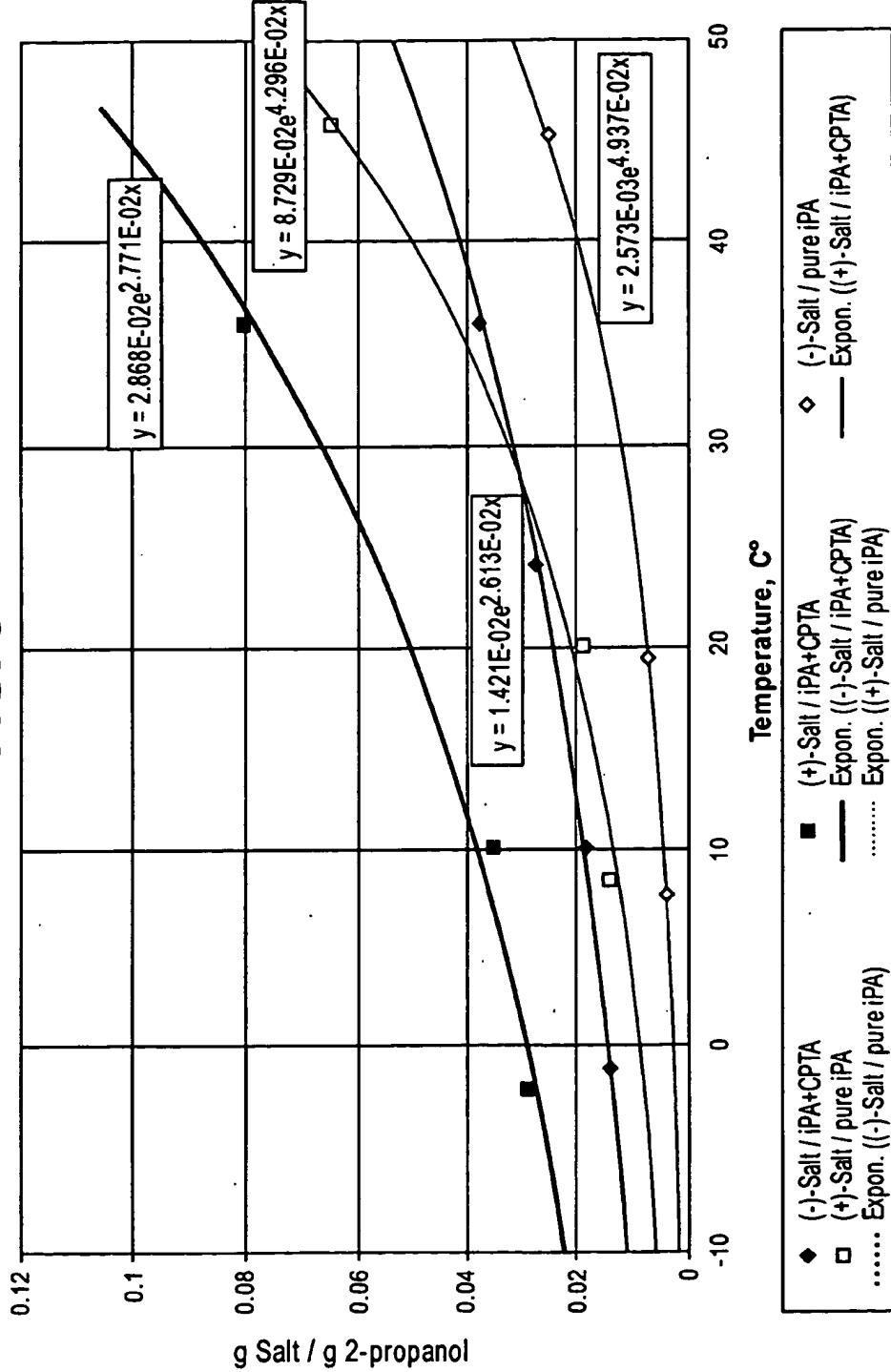
Exp. #	Charge		Nucl'n Temp.	Product Isolation: Ratio of % (-)-CPTA		Calculated % Yield of (-)-CPTA	Comments
	g iPA/ g CPTA	mole base/ mole CPTA		Crystal	M.L.		
1	4.11	0.57	61°	17° + 6hr	79.9	27.0	69.5 (+)-Salt nucleation at 22°
2	4.11	0.55	59°	22° + 8hr	77.9	28.3	68.2 (+)-Salt nucleation after 1 hr at 22°
3	4.11	0.90	59°	40°	99.2	27.7	61.9 initially added 0.15 eq. triethylamine
4	5.50	0.75	61°	22° + 10hr	66.4	30.7	71.8 (+)-Salt nucleation at 40°
				to 28°	68.2	28.8	73.4
				to 35°	71.4	29.1	70.6
				to 43°	77.0	29.9	65.7
				to 51°	95.0	30.3	57.9
				to 55°	99.4	33.0	50.9
5	4.11	0.52	61°	13° + 8hr	99.7	20.9	73.6 (+)-Salt nucleation 3 hr after sample
				+30hr(13°)	83.3	24.9	71.6
6	3.14	0.52	59°	1°	98.7	23.5	69.6
				+20hr(1°)	98.2	19.4	76.3
				to 17° + 9hr	81.2	25.3	71.8
7	5.50	0.90	64°	3° + 1hr	66.4	25.5	79.6 initially added 0.04 eq. KOH
				to 22° + 10hr	~56	25.5	90.0
8	3.53	0.55	59°	22° + 5hr	78.6	26.0	71.7 (+)-Salt nucleation at 30°
9	3.93	0.45	59°	22° + 4hr	99.6	24.3	68.0
				+12hr(22°)	99.5	22.9	70.4
	0.52 (added base)			(22°) + 3hr	89.4	24.6	70.1 (+)-Salt nucleating, not at equilibrium
	0.49 (added CPTA)			(22°) + 22hr	84.3	25.9	69.6
10	3.53	0.52	59°	22° + 10hr	73.9	25.5	74.8 (+)-Salt nucleation at 25°
11	3.93	0.45	54°	22° + 14hr	99.1	22.6	71.0
	0.48 (added base)			22° + 24hr	89.2	24.7	70.0
12	3.93	0.43	52°	21°	99.5	27.5	62.2
				+16hr(21°)	99.4	23.9	68.7 seeded with (+)-Salt after sample
				+8hr(22°)	99.3	23.7	69.1
	0.45 (added base)			22° + 14hr	98.9	22.5	71.2 seeded with (+)-Salt after sample
				+6hr(22°)	98.7	22.3	71.61
	0.47 (added base)			22° + 14hr	98.8	21.9	72.6 seeded with (+)-Salt after sample
				+23hr(22°)	92.3	23.4	71.3
13	3.14	0.38	59°	17° + 8hr	99.4	27.2	62.8
				to -10° + 19hr	99.8	24.3	67.9 seeded with (+)-Salt after reaching 10°

FIG. 2

REPLACEMENT SHEET

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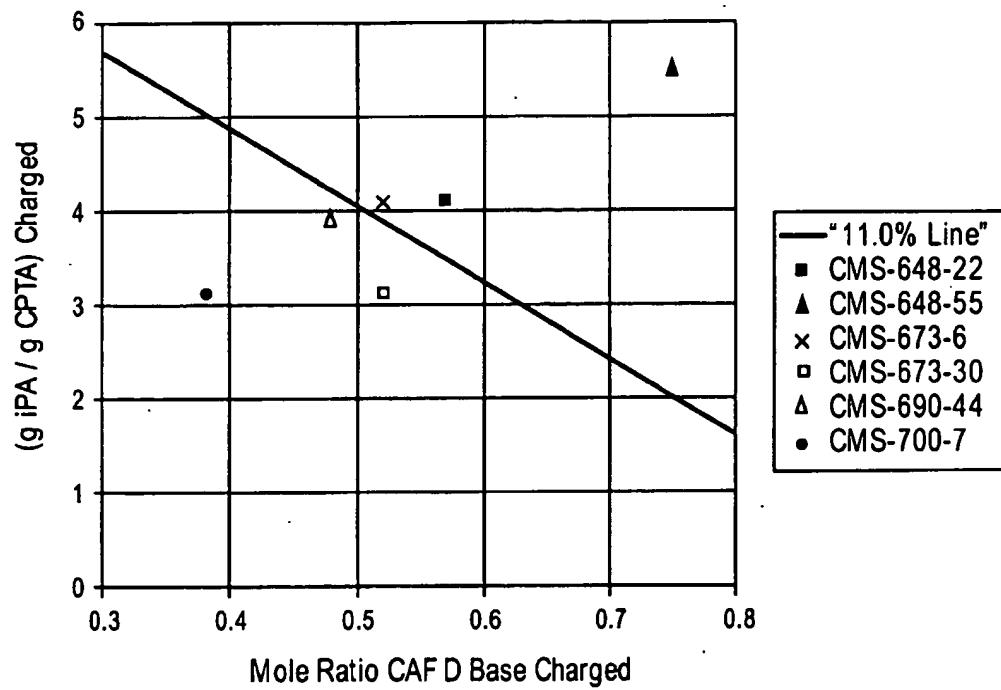
FIG. 3



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**FIG. 4**



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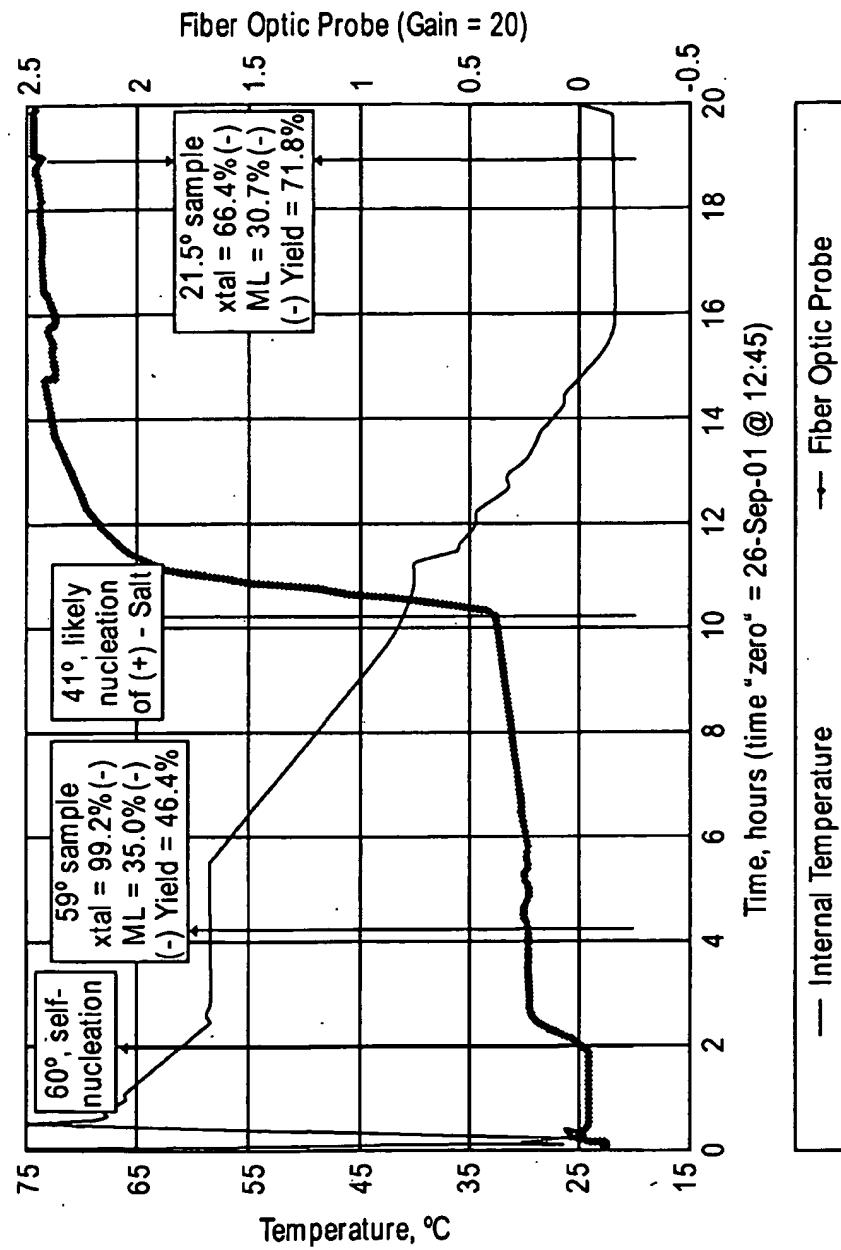


FIG. 5

## REPLACEMENT SHEET

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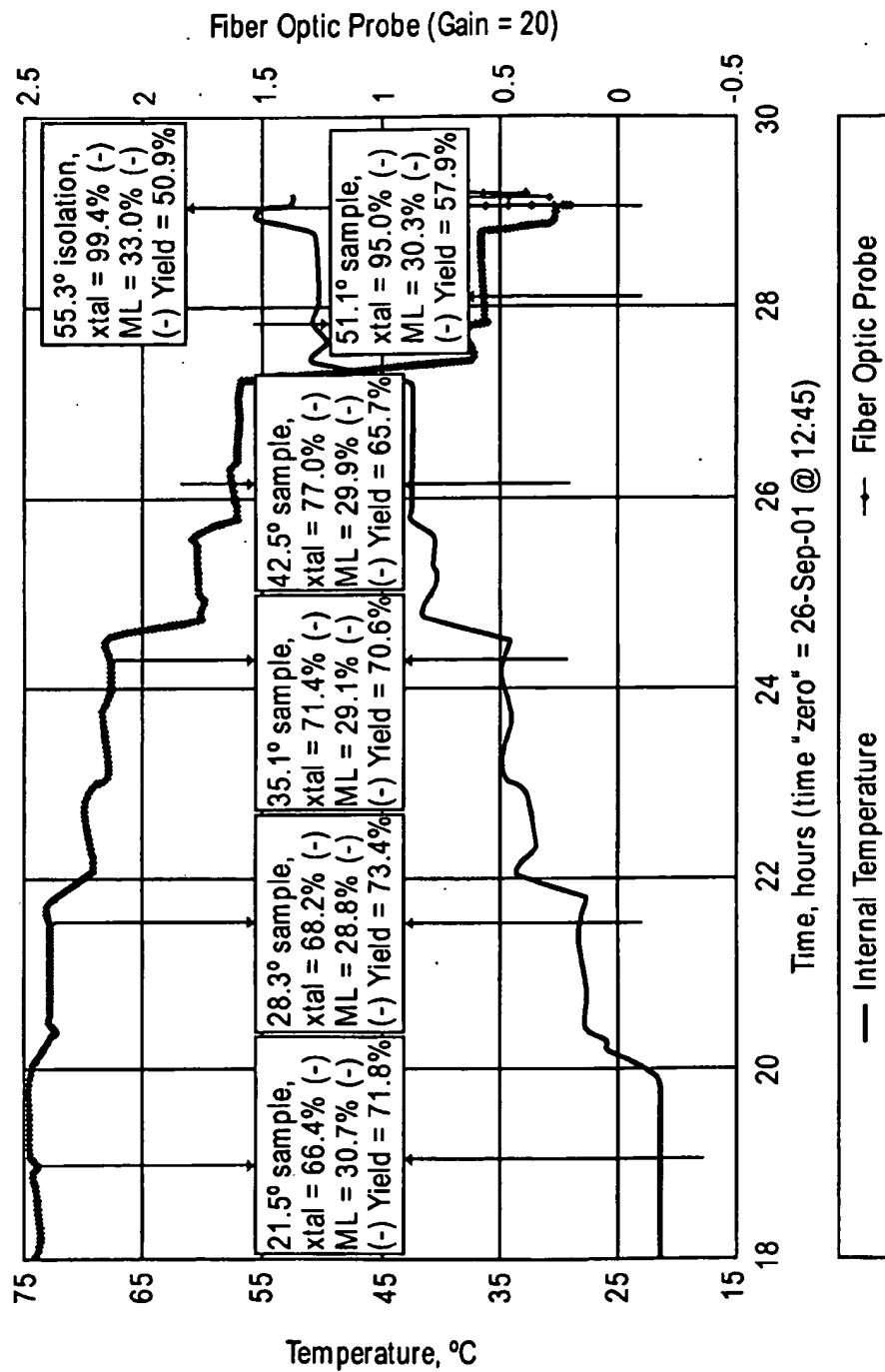


FIG. 5 (CONT.)

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Temperature	Measured Component	Experimental Result	Calculation By Model
21.5 °C	Ratio % (-) - CPTA in crystal	66.4%	63.9%
	Ratio % (-) - CPTA in mother liquor	30.7%	28.5%
	% (-) - CPTA yield	71.8%	72.8%
28.3 °C	Ratio % (-) - CPTA in crystal	68.2%	68.2%
	Ratio % (-) - CPTA in mother liquor	28.8%	28.7%
	% (-) - CPTA yield	73.4%	73.6%
35.1 °C	Ratio % (-) - CPTA in crystal	71.4%	71.4%
	Ratio % (-) - CPTA in mother liquor	29.1%	28.9%
	% (-) - CPTA yield	70.6%	70.8%
42.5 °C	Ratio % (-) - CPTA in crystal	77.0%	76.7%
	Ratio % (-) - CPTA in mother liquor	29.9%	29.1%
	% (-) - CPTA yield	65.7%	67.4%
51.1 °C	Ratio % (-) - CPTA in crystal	95.0%	87.3%
	Ratio % (-) - CPTA in mother liquor	30.3%	29.2%
	% (-) - CPTA yield	57.9%	62.4%
55.3 °C	Ratio % (-) - CPTA in crystal	99.4%	96.1%
	Ratio % (-) - CPTA in mother liquor	33.0%	29.3%
	% (-) - CPTA yield	50.9%	59.6%

FIG. 6

REPLACEMENT SHEET

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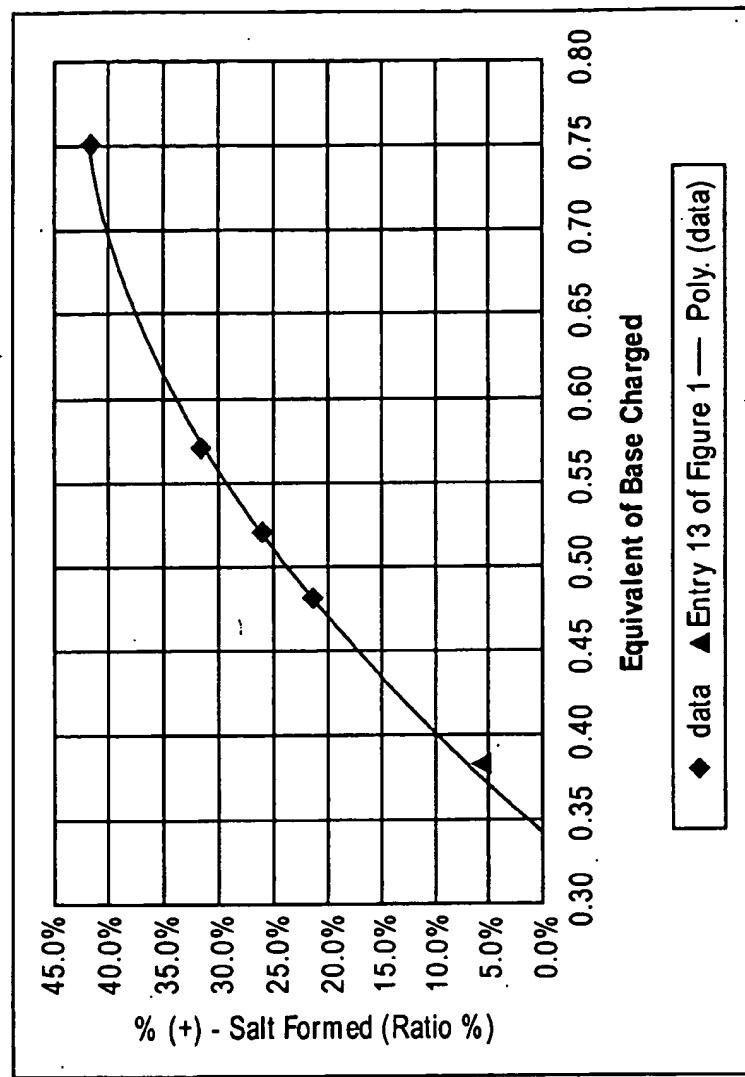


FIG. 7

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## REPLACEMENT SHEET

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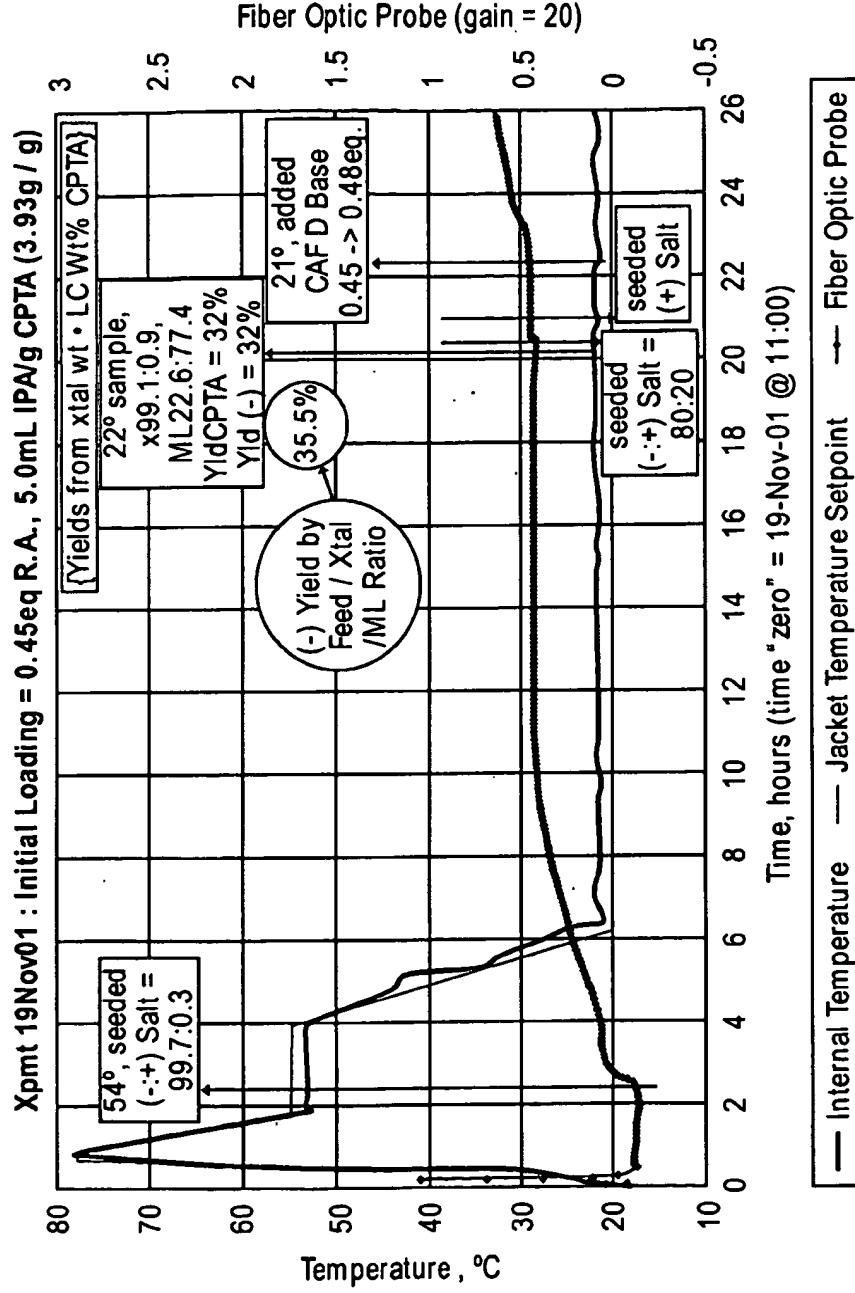
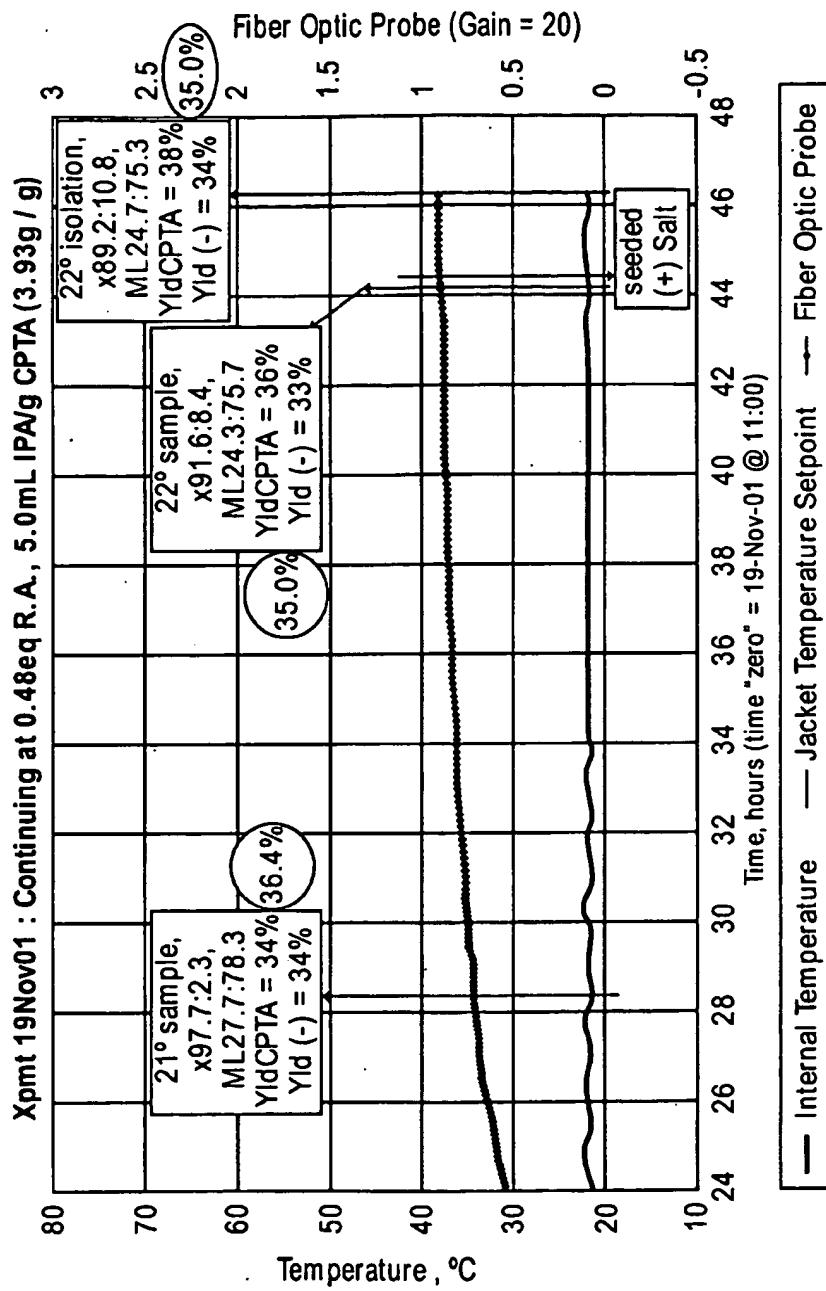


FIG. 8

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**FIG. 8 (CONT.)**

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## REPLACEMENT SHEET

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Component	Normalized Wt% (as CPTA) in Mother Liquor	
	By Work-up	By Model
(-)-Salt	28%	20%
(+)-Salt	41%	44%
(-)-CPTA	7%	9%
(+)-CPTA	24%	27%

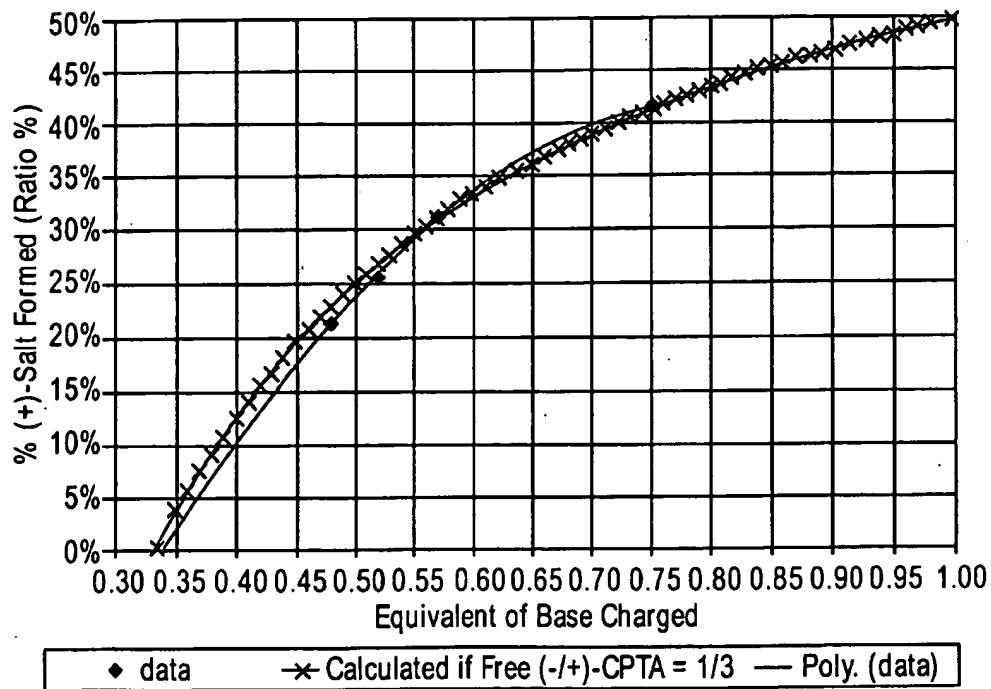


FIG. 9

**REPLACEMENT SHEET**

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(-) -CPTA • CAF D Base Salt :m.p. 180.5 - 181.5

Calculated Values								
	Temp. °C	grams w/soin late	grams evap'd soin	grams soil volat.	grams solids	grams CPTA	wt% solute in evap solv	g solute
Solvent								
iPA w/CPTA	36	17.2900	18.0100	17.3895	0.7200	0.6205	0.0995	0.0228
iPA w/CPTA	24	16.7808	17.5728	16.8840	0.7920	0.6888	0.1032	0.0851
iPA w/CPTA	10	17.2556	18.1769	17.3702	0.9223	0.8067	0.1146	0.0997
iPA w/CPTA	-1	17.1063	17.9898	17.2131	0.8835	0.7767	0.1068	0.0960
EtOH w/CPTA	36	17.1900	17.9419	17.3577	0.7519	0.5842	0.1677	0.0912
EtOH w/CPTA	24	17.2524	17.9330	17.3813	0.6806	0.5517	0.1289	0.0861
EtOH w/CPTA	10	17.2977	18.1608	17.4587	0.8631	0.7021	0.1610	0.1096
EtOH w/CPTA	-1	17.1536	18.2098	17.3383	1.0562	0.8715	0.1847	0.1360

(+) -CPTA • CAF D Base Salt

Calculated Values								
	Temp. °C	grams w/soin late	grams evap'd soin	grams soil volat.	grams solids	grams CPTA	wt% solute in evap solv	g solute
Solvent								
iPA w/CPTA	-2	17.2325	17.8545	17.3147	0.6220	0.5398	0.0822	0.0667
iPA w/CPTA	10	17.1810	17.7942	17.2649	0.6132	0.5293	0.0839	0.0654
iPA w/CPTA	22	17.2838	18.0462	17.4053	0.7624	0.6409	0.1215	0.0792
iPA w/CPTA	36	17.1474	17.8976	17.2742	0.7502	0.6234	0.1268	0.0771
EtOH w/CPTA	10	17.2816	17.4692	17.3074	0.1876	0.1618	0.0258	0.0200
EtOH w/CPTA	-2	17.3289	18.5380	17.6105	1.2091	0.9275	0.2816	0.1448
EtOH w/CPTA	10	17.2118	17.9940	17.4089	0.7822	0.5851	0.1971	0.0913
EtOH w/CPTA	22	17.2095	18.0054	17.4362	0.7959	0.5692	0.2267	0.0889
EtOH w/CPTA	36	17.2133	17.9657	17.4487	0.7524	0.5170	0.2354	0.0807

**FIG. 10A**

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<u>Eq. Base</u>	<u>Predicted k</u>	<u>Regression k used</u>	<u>Regression % (+)-Salt</u>	<u>Free CPTA, Ratio % (+)</u>
0.75	<1	0.68	41.9	25.8
0.57	<1	0.85	31.4	25.3
0.52	<1	0.70	25.7	23.7
0.52	>1	0.60	26.1	24.1
0.48	>1	0.50	21.5	23.7

Experimental Data for Figure 6

**FIG. 10A (CONT.)**

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**FIG. 10B**

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## REPLACEMENT SHEET

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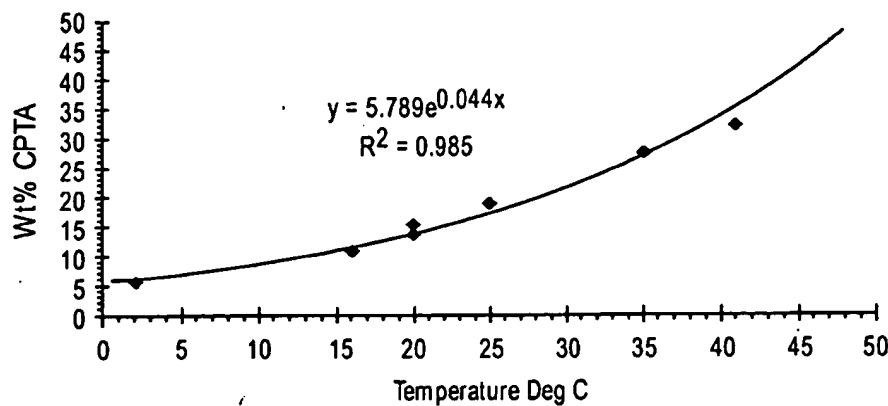


FIG. 11

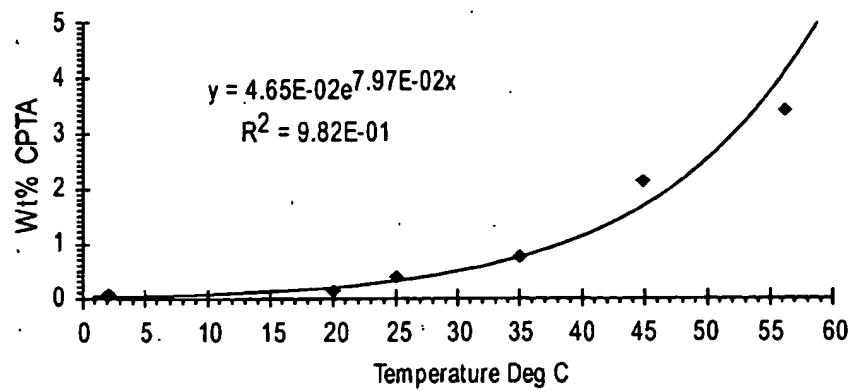


FIG. 12

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## REPLACEMENT SHEET

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Exp. #	Mol Ratio Base	g IPA/ g CPTA	Cool at °C/min	Final T °C	Solid % (-)	Solid % (+)	M.L. % (-)	M.L. % (+)	% Yield Calc	% Yield Overall	% Yield Actual
1	0.53	4.00	0.25	4	90.72	9.28	20.61	79.39	41.9		
Recrystallization		4.00	0.25-1.0	2	99.38	0.62	42.60	57.40	84.7	35.5	34.5
2	0.50	6.17	0.05	.3	98.05	1.95	24.05	75.95	35.1	35.1	
3	0.53	4.00	0.25	0	73.14	26.86	28.88	71.12	47.7		
Recrystallization		4.00	1.0	11	98.20	1.80	22.62	77.38	66.8	31.9	33.0
4	0.54	4.00	0.25	.4	79.72	20.28	26.62	73.38	44.0		
Recrystallization		3.63	0.08	4	99.07	0.93	23.22	76.78	74.5	32.8	32.8
5	0.53	4.00	0.5	-11	93.70	6.30	26.00	74.00	35.4		
Recrystallization		3.93	0.5	.3	99.68	0.33	46.42	53.58	88.8	31.5	31.6
6	0.53	3.98	0.25	.3	90.88	9.12	26.95	73.05	36.1		
Recrystallization		4.98	0.1	4	99.42	0.58	23.85	76.15	88.7	32.0	31.5
7	0.54	4.08	0.3	-3	96.00	4.00	nd	nd			
Recrystallization		4.24	0.4	4	99.86	0.14	57.41	42.59	90.9	-	31.2
8	0.53	4.00	0.25	-8	73.54	26.46	28.09	71.91	48.2		
Recrystallization		3.96	0.3	11	98.57	1.43	21.84	78.16	67.4	32.5	31.1
9	0.50	3.88	0.08	-7	76.83	23.17	28.96	71.04	43.9		
Recrystallization		4.62	0.5	5	98.48	1.52	24.91	75.09	70.6	31.0	30.7
10	0.50	3.90	0.05	0	96.15	3.85	26.07	73.93	34.1		
Recrystallization		4.30	0.3	3	99.86	0.14	70.32	29.68	87.4	29.9	30.6
11	0.55	6.16	0.2	5	73.92	26.08	nd	nd			
Recrystallization		4.38	0.08	12	99.31	0.69	41.08	58.92	56.4	-	29.1
12	0.56	4.99	0.1	2	78.92	21.08	28.04	71.96	43.2		
Recrystallization		5.00	0.25	4	84.47	15.53	29.29	70.71	89.9	(38.8)	(38.3)
Recrystallization		5.00	0.25	12	99.44	0.56	30.30	69.70	78.4	30.4	28.2

nd - Not Determined

FIG. 13

## REPLACEMENT SHEET

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Exp. # (Fig. 1)	Initial T °C	Rate °C/min	Final T °C	Hrs at < 10 °C	Holding Period Profile	Solid		M.L.	% Yield (+)-CPTA
						% (-)	% (+)		
1	60	0.25	4	14	13h at 4C	90.72	9.28	20.61	79.39
8	60	0.25	-5	20	11h to 10C; 3h to -8C, 5h at -8C	73.54	26.46	28.09	71.91
4	55	0.25	-4	3	1h at -4C	79.72	20.28	26.62	73.38
3	60	0.25	-2	16	11h to 10C; 1h to -2C, 4h at -2C	73.14	26.86	28.88	71.12
2	55	0.05	-3	5	1h at -3C	98.05	1.95	24.05	75.95
12	55	0.10	1	13	9h to 10C; 1h to 1C; 4h at 1C	78.92	21.08	28.04	71.97
9	65	0.075	0	8	3h at 0C; 1h to -7C; 2h at -7C	76.83	23.17	28.96	71.04
5	60	0.5	-11	2.5	1.5h at -11C	93.70	6.30	26.00	74.00
10	55	0.05	0	4	1h at 0C	96.15	3.85	26.07	73.93
5	55	0.25	-3	2	1h at -3C	90.88	9.12	26.95	73.05

FIG. 14

	% ee		HPLC Area% Crude	HPLC Area% Isolated	Halofenate	CPTA	Yield	mol % in ML	
	CPTA	(-)-halofenate						Halofenate	
1	97.1	99.9	6.1	85.2	0.72	98.93	55%	5.8%	38%
2	99.3	>99.8	5.5	89.6	0.60	99.40	52%	5.9%	41%
Second Crop	99.6	6.1	45.0	3.89	89.93	21%	4.3%	13%	
3	99.2	99.7	7.1	85.3	0.40	99.29	55%	7.5%	34%
4	98.6	99.8	3.9	91.8	0.10	99.90	47%	3.1%	40%
Second Crop	98.8	6.1	82.5	3.22	89.65	33%	nd	nd	
5	99.7	99.7	8.0	83.2	0.64	99.18	59%	nd	

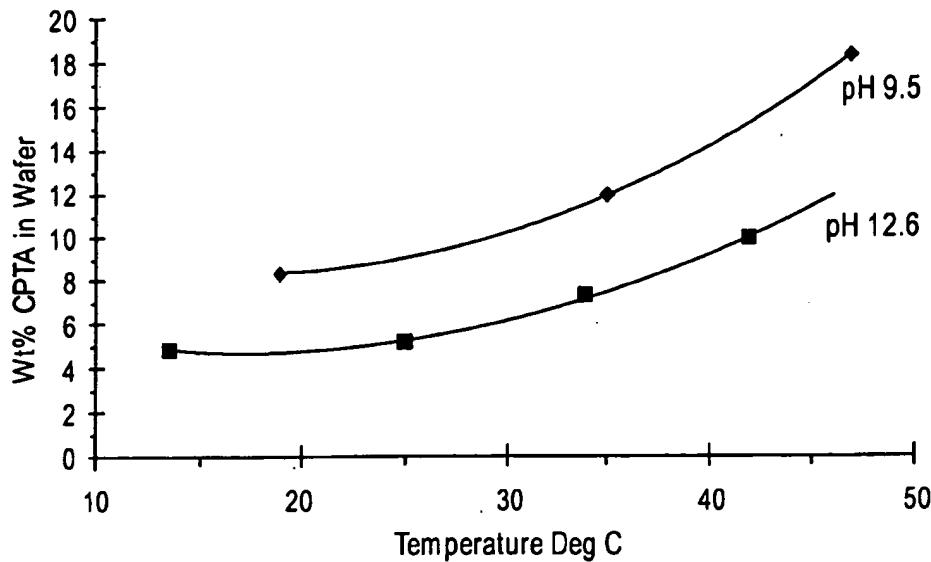
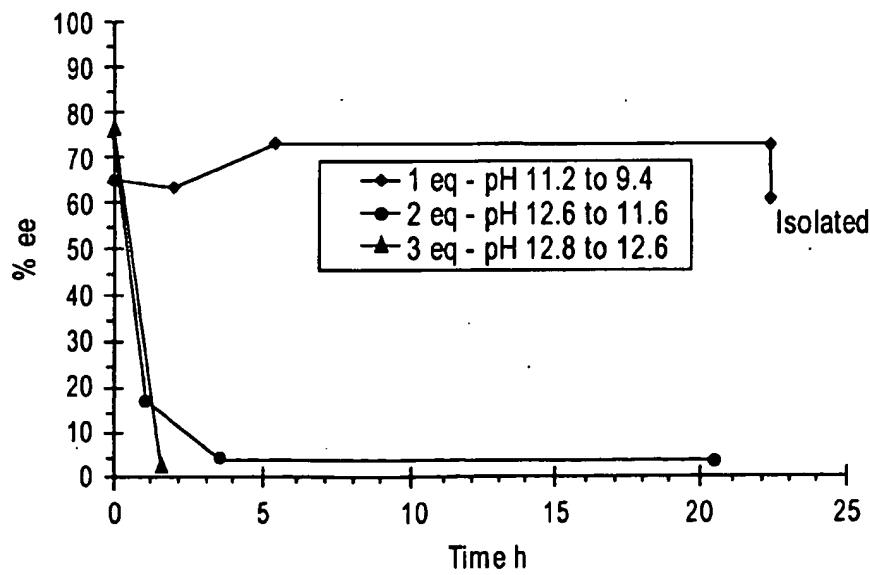
nd - Not Determined

FIG. 15

Class  
560Subclass  
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## REPLACEMENT SHEET

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**FIG. 16****FIG. 17**

## REPLACEMENT SHEET

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Recovered From:	Wt% Aqueous SiN	pH	mp °C	Recovery (+)/(-) Ratio
Diastereomeric Salt	20.4	12.4	157.2-158.0	97% 0.1/99.9
"	20.1	12.1	160.4-161.0	98%
"	19.6	nd	164.0-164.6	92%
"	11.9	13.2	161.8-162.6	94%
"	4.1	12	164.0-164.6	88% 0.1/99.9
Resolution ML	13.9	13	159.2-159.6	62%
"	11.0	12.3	162.4-163.0	87%
Combined ML & Salt	19.9	13	162.6-163.4	85%
TCI Americas Lot# FHG01		165.6-166.4		0.1/99.9

FIG. 18

Solvent	Temp °C	Sample weight g	Sample Volume mL	Wt% CPTA in Solution
1,2-Dichloroethane	41	0.1558	25.00	32.3
	35	0.1360	25.00	27.6
	25	0.1455	10.00	18.8
	20	0.0489	25.00	15.3
	20	0.0505	10.00	14.0
	16	0.3230	25.00	11.0
	2.1	0.1300	10.00	6.05
Hepiane	56	0.4641	25.00	3.39
	45	0.3331	25.00	2.11
	35	0.3823	25.00	0.767
	25	0.6750	25.00	0.413
	20	0.1994	10.00	0.17
	2.1	0.6038	25.00	0.057

FIG. 19

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## REPLACEMENT SHEET

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pH	Temp °C	Sample weight g	Sample Volume mL	Wt% CPTA in Solution
9.4	35	0.3036	25.00	11.86
9.7	47	0.1111	25.00	18.28
9.5	19	0.2290	25.00	8.33
12.7	13.5	0.2012	25.00	4.89
12.6	25	0.3538	25.00	5.18
12.5	34	0.2320	25.00	7.30
12.5	42	0.3055	25.00	9.91

FIG. 20

Wt Loaded g	50% NaOH	Reflux Time	pH	HPLC Area%	(+)/( -)	Assay	% CPTA	Isolated
(+)-Halofenate								
8.65	1.67 (1 eq)	0 h	11.2	71.9/15.1				
		2		78.3/17.2				
		5.5		80.6/12.4				
		22.5	9.4	84.1/13.4				
		Oil		80.3/19.6		92%	81%	
6.94	2.68 (2 eq)	0	12.6	83.4/11.3				
		1		56.8/40.4				
		3.5		49.0/45.0				
		20.5	11.6	47.5/45.0				
		Oil		48.7/51.0		103%	94%	
7.28	4.21 (3 eq)	0	12.8	80.4/10.5				
		1.5	12.6	49.6/47.0				
		Oil		47.3/52.5		102%	88%	

FIG. 21